

53-07-03

1637

PTO/SB/21 (08-00)

Approved for use through 10/31/02. OMB 0651-0031

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**TRANSMITTAL  
FORM**

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Total Number Of Pages In This Submission

101 pages + 3  
references +  
Tabs A & B

Application Number

09/402,244

Filing Date

December 12, 2000

First Named Inventor

Paul A. INSEL

Group Art Unit

1637

Examiner Name

J. Fredman

Attorney Docket No.

220002058901

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**ENCLOSURES (check all that apply)**☒ Fee Transmittal Form + duplicate  
copy for fee processing - 2 pages☐ Fee Attached☒ Amendment / Reply - 35 pages☐ After Final☐ Affidavits/declarations☒ Extension of Time Request - 1 page☐ Express Abandonment Request☒ Information Disclosure Statement  
(Supplemental) - 3 pages☐ Certified Copy of Priority Document(s)☐ Response to Missing Parts/  
Incomplete Application☐ Response to Missing Parts  
under 37 CFR 1.52 or 1.53☐ Assignment Papers  
(for an Application)☐ Drawing(s)☐ Licensing-related Papers☐ Petition☐ Petition to Convert to a  
Provisional Application☐ Power of Attorney, Revocation  
Change of Correspondence Address☐ Terminal Disclaimer☐ Request for Refund☐ CD, Number of CD(s) \_\_\_\_\_☐ After Allowance Communication to  
Group☐ Appeal Communication to Board of  
Appeals and Interferences☐ Appeal Communication to Group  
(Appeal Notice, Brief, Reply Brief)☐ Proprietary Information☐ Status Letter☒ Other Enclosure(s) (please identify  
below):

1. Substitute Specification, including Tab  
A - 29 pages + side tab
2. Marked-up version of the Substitute  
Specification showing changes,  
including Tab B - 30 pages + side tab
3. Form PTO-1449 + duplicate copy - 2  
pages
4. Three (3) references
5. Return receipt postcard

Remarks

**SIGNATURE OF APPLICANT, ATTORNEY OR AGENT**

Firm

Morrison &amp; Foerster LLP, 755 Page Mill Road, Palo Alto, California 94304-1018

or

Individual Name

Debra J. Glaister (Registration No. 33,888)

Signature

Date

March 5, 2003

**CERTIFICATE OF MAILING BY "EXPRESS MAIL"**

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Date of Deposit: March 5, 2003


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Tamara Alcaraz

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pa-770763

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 <p><b>FEE TRANSMITTAL FOR FY 2003</b></p> <p><i>Effective 01/01/2003. Patent fees are subject to annual revision.</i></p>	<b>Complete if Known</b>	
	Application Number	09/402,244
	Filing Date	December 12, 2000
	First Named Inventor	Paul A. INSEL
	Examiner Name	J. Fredman
Group Art Unit	1637	
<b>TOTAL AMOUNT OF PAYMENT</b>		<b>(\$663.00)</b>
		Attorney Docket No. 220002058901

<p><b>METHOD OF PAYMENT</b></p> <p>1. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to:</p> <p>Deposit Account Number: 03-1952</p> <p>Deposit Account Name: Morrison &amp; Foerster LLP</p> <p><input checked="" type="checkbox"/> Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17</p> <p><input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27</p> <p>2. <input type="checkbox"/> Payment Enclosed:</p> <p><input type="checkbox"/> Check <input type="checkbox"/> Credit Card <input type="checkbox"/> Money Order <input type="checkbox"/> Other</p>	<p><b>FEE CALCULATION (continued)</b></p> <p><b>3. ADDITIONAL FEES</b></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Large Fee Code</th> <th>Entity Fee (\$)</th> <th>Small Fee Code</th> <th>Entity Fee (\$)</th> <th>Fee Description</th> <th>Fee Paid</th> </tr> </thead> <tbody> <tr><td>1051</td><td>130</td><td>2051</td><td>65</td><td>Surcharge - late filing fee or oath</td><td></td></tr> <tr><td>1052</td><td>50</td><td>2052</td><td>25</td><td>Surcharge - late provisional filing fee or cover sheet</td><td></td></tr> <tr><td>1053</td><td>130</td><td>1053</td><td>130</td><td>Non-English specification</td><td></td></tr> <tr><td>1812</td><td>2,520</td><td>1812</td><td>2,520</td><td>For filing a request for <i>ex parte</i> reexamination</td><td></td></tr> <tr><td>1804</td><td>920*</td><td>1804</td><td>920*</td><td>Requesting publication of SIR prior to Examiner action</td><td></td></tr> <tr><td>1805</td><td>1,840*</td><td>1805</td><td>1,840*</td><td>Requesting publication of SIR after Examiner action</td><td></td></tr> <tr><td>1251</td><td>110</td><td>2251</td><td>55</td><td>Extension for reply within first month</td><td></td></tr> <tr><td>1252</td><td>410</td><td>2252</td><td>210</td><td>Extension for reply within second month</td><td></td></tr> <tr><td>1253</td><td>930</td><td>2253</td><td>465</td><td>Extension for reply within third month</td><td>465</td></tr> <tr><td>1254</td><td>1,450</td><td>2254</td><td>725</td><td>Extension for reply within fourth month</td><td></td></tr> <tr><td>1255</td><td>1,970</td><td>2255</td><td>985</td><td>Extension for reply within fifth month</td><td></td></tr> <tr><td>1401</td><td>320</td><td>2401</td><td>160</td><td>Notice of Appeal</td><td></td></tr> <tr><td>1402</td><td>320</td><td>2402</td><td>160</td><td>Filing a brief in support of an appeal</td><td></td></tr> <tr><td>1403</td><td>280</td><td>2403</td><td>140</td><td>Request for oral hearing</td><td></td></tr> <tr><td>1451</td><td>1,510</td><td>1451</td><td>1,510</td><td>Petition to institute a public use proceeding</td><td></td></tr> <tr><td>1452</td><td>110</td><td>2452</td><td>55</td><td>Petition to revive - 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late filing fee or oath		1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet		1053	130	1053	130	Non-English specification		1812	2,520	1812	2,520	For filing a request for <i>ex parte</i> reexamination		1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action		1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action		1251	110	2251	55	Extension for reply within first month		1252	410	2252	210	Extension for reply within second month		1253	930	2253	465	Extension for reply within third month	465	1254	1,450	2254	725	Extension for reply within fourth month		1255	1,970	2255	985	Extension for reply within fifth month		1401	320	2401	160	Notice of Appeal		1402	320	2402	160	Filing a brief in support of an appeal		1403	280	2403	140	Request for oral hearing		1451	1,510	1451	1,510	Petition to institute a public use proceeding		1452	110	2452	55	Petition to revive - unavoidable		1453	1,300	2453	650	Petition to revive - unintentional		1501	1,300	2501	650	Utility issue fee (or reissue)		1502	470	2502	235	Design issue fee		1503	630	2503	315	Plant issue fee		1460	130	1460	130	Petitions of the Commissioner		1807	50	1807	50	Petitions related to provisional applications		1806	180	1806	180	Submission of Information Disclosure Stmt	180	8021	40	8021	40	Recording each patent assignment per properties (times number of properties)		1809	750	2809	375	Filing a submission after final rejection (37 CFR § 1.129(a))		1810	750	2810	375	For each additional invention to be examined (37 CFR § 1.129(b))		1801	750	2801	375	Request for Continued Examination (RCE)		1802	900	1802	900	Request for expedited examination of a design application	
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<p><b>1. BASIC FILING FEE</b></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Large Fee Code</th> <th>Entity Fee (\$)</th> <th>Small Fee Code</th> <th>Entity Fee (\$)</th> <th>Fee Description</th> <th>Fee Paid</th> </tr> </thead> <tbody> <tr><td>1001</td><td>750</td><td>2001</td><td>375</td><td>Utility filing fee</td><td></td></tr> <tr><td>1002</td><td>330</td><td>2002</td><td>165</td><td>Design filing fee</td><td></td></tr> <tr><td>1003</td><td>510</td><td>2003</td><td>255</td><td>Plant filing fee</td><td></td></tr> <tr><td>1004</td><td>750</td><td>2004</td><td>375</td><td>Reissue filing fee</td><td></td></tr> <tr><td>1005</td><td>160</td><td>2005</td><td>80</td><td>Provisional filing fee</td><td></td></tr> </tbody> </table> <p style="text-align: right;"><b>SUBTOTAL (1) (\$0.00)</b></p> <p><b>2. EXTRA CLAIM FEES</b></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Total Claims</th> <th>38</th> <th>- 36** =</th> <th>2</th> <th>x</th> <th>9</th> <th>=</th> <th>\$18</th> </tr> </thead> <tbody> <tr> <td>Independent Claims</td> <td>2</td> <td>- 3** =</td> <td>0</td> <td>x</td> <td>42</td> <td>=</td> <td>\$0</td> </tr> <tr> <td>Multiple Dependent</td> <td></td> <td></td> <td></td> <td></td> <td>140</td> <td>=</td> <td>\$0</td> </tr> </tbody> </table> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Large Fee Code</th> <th>Entity Fee (\$)</th> <th>Small Fee Code</th> <th>Entity Fee (\$)</th> <th>Fee Description</th> <th>Fee Paid</th> </tr> </thead> <tbody> <tr><td>1202</td><td>18</td><td>2202</td><td>9</td><td>Claims in excess of 20</td><td></td></tr> <tr><td>1201</td><td>84</td><td>2201</td><td>42</td><td>Independent claims in excess of 3</td><td></td></tr> <tr><td>1203</td><td>280</td><td>2203</td><td>140</td><td>Multiple dependent claims, if not paid</td><td></td></tr> <tr><td>1204</td><td>84</td><td>2204</td><td>42</td><td>**Reissue independent claims over original patent</td><td></td></tr> <tr><td>1205</td><td>18</td><td>2205</td><td>9</td><td>**Reissue claims in excess of 20 and over original patent</td><td></td></tr> </tbody> </table> <p style="text-align: right;"><b>SUBTOTAL (2) (\$18.00)</b></p>	Large Fee Code	Entity Fee (\$)	Small Fee Code	Entity Fee (\$)	Fee Description	Fee Paid	1001	750	2001	375	Utility filing fee		1002	330	2002	165	Design filing fee		1003	510	2003	255	Plant filing fee		1004	750	2004	375	Reissue filing fee		1005	160	2005	80	Provisional filing fee		Total Claims	38	- 36** =	2	x	9	=	\$18	Independent Claims	2	- 3** =	0	x	42	=	\$0	Multiple Dependent					140	=	\$0	Large Fee Code	Entity Fee (\$)	Small Fee Code	Entity Fee (\$)	Fee Description	Fee Paid	1202	18	2202	9	Claims in excess of 20		1201	84	2201	42	Independent claims in excess of 3		1203	280	2203	140	Multiple dependent claims, if not paid		1204	84	2204	42	**Reissue independent claims over original patent		1205	18	2205	9	**Reissue claims in excess of 20 and over original patent		<p><b>4. SUBMITTED BY</b></p> <p>Name (Print/Type): Debra J. Glaister</p> <p>Registration No. (Attorney/Agent): 33,888</p> <p>Telephone: (650) 813-5725</p> <p>Signature: <i>Debra J. Glaister</i></p> <p>Date: March 5, 2003</p>
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PATENT  
Docket No. 220002058901  
Client Ref. UC 98-021-3

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Tamara Alcaraz

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Paul A. INSEL et al.

Serial No.: 09/402,244

Filing Date: December 12, 2000

For: METHODS AND COMPOSITIONS FOR  
IDENTIFYING VARIATIONS IN  
HUMAN  $\alpha_{1B}$ - AND  $\beta_2$ - ADRENERGIC  
RECEPTOR GENES

Examiner: J. Fredman

Group Art Unit: 1637

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AMENDMENT UNDER 37 C.F.R. §1.111

Assistant Commissioner for Patents  
Washington, D.C. 20231

Dear Sir:

This is in response to the non-final Office Action dated September 5, 2002 (Paper No. 15) for which a response was due on December 5, 2002. Filed herewith is a Petition and fee for a three-month extension of time thereby extending the deadline for response from December 5, 2002 to March 5, 2003. Accordingly, this response is timely filed.

Applicants submit concurrently herewith a Substitute Specification, attached hereto as Tab A, and marked up version of the Substitute Specification showing changes, attached hereto as Tab B; and a Supplemental Information Disclosure Statement along with Form PTO-1449, three references and the appropriate fee.

03/11/2003 YPO/LITEL 00000007 03/15/02 09402244

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pa-729634

## AMENDMENTS

### In the Specification:

Applicants are submitting concurrently herewith a Substitute Specification pursuant to 37 C.F.R. 1.125(b) in order to correct an inadvertent word processing error to Greek symbols that occurs throughout the text of the specification of record. In particular, in the PCT publication, WO 99/24454, the correct notation of  $\alpha_{1B}$ -AR was converted to  $I_{1B}$ -AR through an inadvertent word processing error. In particular, in the PCT publication WO 99/24454, the correct notation of  $\beta_2$ -AR was converted to  $\vartheta_2$ -adrenergic receptors through an inadvertent word processing error. The Substitute Specification is being submitted in order to correct these inadvertent word processing errors.

Please amend paragraph [0023] of the Substitute Specification as follows:

(Amended)

Figure 5 (SEQ ID NO:11) depicts the sequence profile of fragment A of the human  $\alpha_{1B}$ -AR gene. The amplified fragments were sequenced with the amplification, primer SEQ ID NO: 1 using Applied Biosystems' DNA sequencer. Each peak indicates a different nucleotide. In some cases "ambiguous reads" (N) occur as the result of duplicate bases (heterozygosity) or reading ambiguities, which can generally be corrected afterwards.

Please amend paragraph [0024] of the Substitute Specification as follows:

(Amended)

Figure 6 (SEQ ID NO:12) depicts the sequence profile of fragment A of the human  $\beta_2$ -AR gene. The amplified fragments were sequenced with the amplification primer SEQ ID NO:6 using Applied Biosystems' DNA sequencer. Each peak indicates a different nucleotide. In some cases "ambiguous reads" (N) occur as the result of duplicate bases (heterozygosity) or reading ambiguities, which can generally be corrected afterwards.

Please amend paragraph [0068] of the Substitute Specification, as follows:

(Amended)

In a preferred embodiment, the method is used for diagnosing nocturnal asthma based on glycine 16 polymorphism in  $\beta_2$ -AR gene. In another embodiment, the method is used for a diagnosis of essential hypertension based on the same genetic polymorphism. While assaying for glycine 16 polymorphism, genomic DNA of the test subject can be obtained from a blood sample. The N-terminal fragment A (as shown in Figure 2) that encompasses sequences encoding the residue glycine 16 can be amplified using primers SEQ ID NOS:5 and 6, or derivatives thereof. Direct sequencing of the amplified products using the same primers employed in the amplification procedure may be performed to detect the single base change (adenosine to guanosine) at position 46 (numbering from the start codon) that results in amino acid substitution of arginine with glycine. Homozygosity of glycine 16 indicates the presence or a predisposition to nocturnal asthma and/or essential hypertension. Glycine 16 homozygotes will be apparent by comparing the sequence peaks from the subject sample to those of the controls (for an example of the sequence output from an automated DNA sequencer, see Figure 5 (SEQ ID NO:11) or 6 (SEQ ID NO:12)). A single peak corresponding to 27 nucleotide guanosine at position 46 is indicative of glycine 16 homozygosity. Two overlapping peaks, each representing guanosine or adenosine respectively at position 46, suggest heterozygosity of glycine 16. Finally, a single peak representing adenosine shows that the subject is homozygous in arginine 16.

Please amend paragraph [0076] of the Substitute Specification, as follows:

(Amended)

#### Example 5

#### Sequence Analysis

The PCR products of expected sizes were cut from the gel and the DNA was purified using QIAquick Gel Extraction Kit. The extracted DNA was resuspended in Tris-EDTA buffer